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(51) International Patent Classification ⁶ : A61K 31/00, 31/44, 31/40, 31/22, 31/365	A3	(11) International Publication Number: WO 99/48488 (43) International Publication Date: 30 September 1999 (30.09.99)
(21) International Application Number: PCT/US99/06396 (22) International Filing Date: 23 March 1999 (23.03.99) (30) Priority Data: 09/046,235 23 March 1998 (23.03.98) US (71) Applicant: CHILDREN'S MEDICAL CENTER CORPORATION [US/US]; 300 Longwood Avenue, Boston, MA 02115 (US). (72) Inventors: YANKNER, Bruce, A.; 299 Prince Street, West Newton, MA 02165 (US). NADEAU, Philip; 38 St. Germain Street #1, Boston, MA 02115 (US). (74) Agent: PABST, Patrea, L.; Arnall Golden & Gregory, LLP, 2800 One Atlantic Center, 1201 West Peachtree Street, Atlanta, GA 30309-3450 (US).		(81) Designated States: AU, CA, JP, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i> (88) Date of publication of the international search report: 22 June 2000 (22.06.00)
(54) Title: METHODS FOR DECREASING BETA AMYLOID PROTEIN (57) Abstract Blood cholesterol levels are correlated with production of amyloid β protein ((A) β), and are predictors of populations at risk of developing AD. Methods for lowering blood cholesterol levels can be used to decrease production of A β , thereby decreasing the risk of developing AD. The same methods and compositions can also be used for treating individuals diagnosed with AD. Methods include administration of compounds which increase uptake of cholesterol by the liver, such as the administration of HMG CoA reductase inhibitors, administration of compounds which block endogenous cholesterol production, such as the administration of HMG CoA reductase inhibitors, administration of compositions which prevent uptake of dietary cholesterol, and administration of combinations of any of these which are effective to lower blood cholesterol levels. Methods have also been developed to predict populations at risk, based on the role of cholesterol in production of A β . For example, individuals with Apo E4 and high cholesterol, defined as a blood cholesterol level of greater than 200 mg/dl, post menopausal women with high cholesterol levels – especially those who are not taking estrogen, or individuals with high blood cholesterol levels who are not obese are all at risk of developing AD if blood cholesterol levels are not decreased.		

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/06396

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K31/00 A61K31/44 A61K31/40 A61K31/22 A61K31/365

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
T	E.R. FREARS ET AL.: "The role of cholesterol in the biosynthesis of beta-amyloid" NEUROREPORT, vol. 10, no. 8, June 1999 (1999-06), pages 1699-1705, XP002117061 the whole document	1-3,5, 7-25,27
E	WO 99 38498 A (WARNER LAMBERT CO ;BISGAIER CHARLES LARRY (US); EMMERLING MARK RIC) 5 August 1999 (1999-08-05) the whole document	1-3,5, 7-25,27
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
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- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

Z document member of the same patent family

Date of the actual completion of the international search

30 September 1999

Date of mailing of the international search report

03.04.00

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 eponl,
Fax: (+31-70) 340-3016

Authorized officer

HOFF, P

INTERNATIONAL SEARCH REPORT

International Application No

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 99 15159 A (NOVA MOLECULAR INC) 1 April 1999 (1999-04-01) abstract page 2, line 22 -page 5, line 14 page 14, line 13 - line 25; claims 1,4-6,12,18,20; example 2 ---	1-3,5, 7-25,27
P,X	WO 98 47518 A (EUROP LAB MOLEKULARBIOLOG ;SIMONS KAI (DE)) 29 October 1998 (1998-10-29) the whole document ---	1-3,5, 7-25,27
X	WO 95 06470 A (MERCK & CO INC ;SCOLNICK EDWARD M (US)) 9 March 1995 (1995-03-09) the whole document ---	1-3,5, 7-25,27
X	G.P. JARVIK ET AL.: "Interactions of apolipoprotein E genotype, total cholesterol level, age, and sex in prediction of Alzheimer's disease" NEUROLOGY, vol. 45, no. 6, 1995, pages 1092-1096, XP002117062 the whole document ---	14-22
A	D.L. SPARKS: "Intraneural beta-Amyloid Immunoreactivity in the CNS" NEUROBIOLOGY OF AGING, vol. 17, no. 2, 1996, pages 291-299, XP002117063 cited in the application the whole document ---	1-3,5, 7-25,27
A	YANKNER B A: "Mechanisms of neuronal degeneration in Alzheimer's disease." NEURON, (1996 MAY) 16 (5) 921-32. REF: 172, XP002117064 cited in the application the whole document ---	1-3,5, 7-25,27
A	WISNIEWSKI T ET AL: "Is Alzheimer's disease an apolipoprotein E amyloidosis?." LANCET, (1995 APR 15) 345 (8955) 956-8., XP002117065 the whole document -----	1-3,5, 7-25,27

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 99/ 06396

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
See FURTHER INFORMATION SHEET PCT/ISA/210
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. Claims: 1(part.), 2, 3, 5(part.), 7-13(all part.), 14-22, 23(part.), 24, 25, 27(part.)
2. Claims: 1(part.), 4, 7-13(all part.), 23(part.), 26, 29(part.)
3. Claims: 1(part.), 5(part.), 7-13(all part.), 23(part.), 27(part.), 28
4. Claims: 1(part.), 6, 7-13(all part.), 23(part.), 29(part.)
5. Claims: 1(part.), 7-13(all part.), 23(part.), 29(part.)

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1(part.), 2, 3, 5(part.), 7-13(all part.), 14-22, 23(part.), 24, 25, 27(part.)

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box 3.

Although claims 1-13 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Further defect(s) under Article 17(2)(a):

Continuation of Box 3.

Present claims 1,2,23,24 relate to a compound defined by reference to a desirable characteristic or property, namely "compound which decreases blood cholesterol levels" or "HMG CoA reductase inhibitor". The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a pharmacological profile or mode of action. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds structurally identified in claims 3 and 25 and the general idea underlying the application.

Claims searched completely: 3,14-22,25

Claims searched incompletely: 1,2,5,7-13,23,24,27

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/06396

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9938498 A	05-08-1999	AU 1616599 A	16-08-1999
WO 9915159 A	01-04-1999	AU 9454098 A	12-04-1999
WO 9847518 A	29-10-1998	DE 19716120 A	22-10-1998
WO 9506470 A	09-03-1995	AU 7397094 A	22-03-1995
		US 5368404 A	29-11-1994